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EXPERIMENTAL STUDIES ON THE TRUE NATURE OF THE SO-CALLED PANCREATECTOMY CELLS.

by

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INTRODUCTION

Studies into histologic changes of the hypophysis after resection of the sexual glands or the thyroid were started in the last century. At the beginning of this century the appearance of castration cells in the hypophysis was remarked after castration by Biedle (rat, 1912), and then that of thyroidectomy cells after thyroidectomy by SATWORNITZKAJA (dog, 1926).

What change will be expected in the hypophysis after total pancreatectomy ? Histologic studies initiated by Kraus (cat, 1922) have failed to demonstrate any special cells like thyroidectomy cells or castration cells.

Recently, YOSHIOKA and KUSAMA (dog, 1954) reported that they happened to observe special cells in the hypophysis appearing after total pancreatectomy, and they named these cells pancreatectomy cells.

The intimate interrelationships of the hypophysis to the other endocrine organs such as the sexual glands, adrenals and thyroid are generally accepted, but the existence of a tropic hormone of the hypophysis towards the pancreas has not yet been ascertained. The discovery of the special cell named pancreatectomy cell, which might be taken as one of the evidences showing the special relation between the hypophysis and the pancreas, provoked much interest among us. In this paper we want to insist from our experimental study that the so-called pancreatectomy cell can not be analogous with the castration cell or the thyroidectomy cell.

YOSHIOKA AND KUSAMA'S "PANCREATECTOMY CELL"

What are the characteristics of the pancreatectomy cell found out by Yoshioka

and Kusama ? Here are summarized the characteristics of the cell, based on their own description :

1. Size and shape : Various sizes, large or small ; round, oval or slender, etc. in shape ; sometimes having processes.

Some nuclei are round ; others oval or slender, etc.

2. Staining attitude : As coarse round granules are observed to be stained metachromatically (deep yellow-brown) with thionine, the cells can be easily identified even through low magnification. Sometimes granules are scanty and accordingly the cytoplasm looks pale. In some cases vacuoles are observed in the cytoplasm.

As the nucleus has gross chromatin granules or a dense nuclear membrane, it is darkly stained.

The cytoplasm shows positive periodic acid Schiff reaction.

3. Distribution : These special cells are widely distributed throughout the hypophysis ; the order in their density is : the pars tuberalis, the intermediate lobe, the posterior lobe, the anterior lobe, and then the eminentia medialis. In the anterior lobe and the pars tuberalis, these cells are present outside the parenchymal cell group, showing the tendency to be located definetely in the intercellular substances. In the posterior lobe a large number of them are observed to be distributed around the blood vessels, but none in the brain substance.

Although it has been much discussed whether the origins of the castration cells and the thyroidectomy cells are the acidophil cells or the basophil cells, they are considered at present to be the hypertrophic vacuolated basophils. Whichever it may be, there remains no doubt that they are originated from the parenchymal cells of the anterior pituitary. But the so-called pancreatectomy cells may not be parenchymal cells, from the standpoint of the mode of their distribution.

RESULTS OF EXPERIMENTS

Sacrificing four dogs by venesection on the 7th, the 14th, the 21st and the 28th day after total pancreatectomy, we removed their hypophysis and fixed in absolute alcohol and embedded in celloidin. Sagittal serial sections were made, each having 15～20 microns thick, and stained with 0.1% thionine solution. To contrast the findings, the same procedures were taken in two cases of pancreato-enterostomized dogs and in six cases of nor al dogs.

To be surprised, the cells stained metachromatically with thionine were observed even in the hypophysis of the normal dogs (although comparatively less in number), and also in the hypophysis of the pancreato-enterostomized dogs. In cases of the normal dogs, the cells, although less in number, are generally, small, slender in shape and mostly have processes. These cells appear abundantly in three cases of the pancreatectomized dogs and in two cases of the pancreato-enterostomized dogs, and most of them are large and oval.

These cells, from the standpoint of their distribution, are deemed to be quite the same ones as so-called pancreatectomy cells. Describing fully the results of our experiments is only the repetition of the preceding description and so only the

findings of the pancreato-enterostomized dog (killed on the 30th day after operation) will be mentioned, and summarized as follows :

The cells with granules stained metachromatically with thionine in the cytoplasm were distributed in quite the same way as Yoshioka and his associates pointed out, but most of them were large and oval, and their nuclei were round and pale. The cells with pycnotic nuclei were discovered in a small number. (Fig. 1). Moreover, showing the same mode of distribution, the cells stained orthochromatically with thionine were discovered, dispersedly or in groups, particularly densely around the transitional zone between the intermediate lobe and the posterior lobe, being arranged characteristically like "clusters of grapes". (Fig. 2). These cells, whose "cartwheel" nuclei were situated eccentrically in the cytoplasm, had pale paranuclear parts, and were considered to be infiltrating plasma cells. Such plasma cell infiltration was clearly recognized in the hypophysis of the pancreatectomized dog killed on the 14th day.

For the sake of contrast, it may be worth while to describe the findings in the other tissues, especially in the liver of normal dogs. The cells stained similarly as those of the hypophysis were distributed dispersedly in the portal space, particularly around the blood vessels. In the liver lobule they were found abundantly around the V. centralis and they infiltrated dispersedly into the interspace among liver cells. A small number of plasma cells were found around the blood vessels. These cells stained metachromatically with thionine were distributed in quite the similar way as those of the hypophysis, so that they may be regarded undoubtedly as the cells of the same kind. (Fig. 3).

As for the findings of the omentum majus, only the photograph is shown for reference. (Fig. 4).

TRUE NATURE OF THE "PANCREATECTOMY CELL"

From the result of our experiments, it was found out that the cells of the same features as so-called pancreatectomy cells were distributed not only in the hypophysis of totally depancreatized dogs, but also in the hypophysis of normal dogs and even in organs other than the hypophysis. Accordingly, the cells named "pancreatectomy cells" are of very common existence and are considered to have an intimate relationship with the intercellular substance.

It is one of the distinctive characteristics of the "pancreatectomy cell" to have cytoplasmic granules stained metachromatically with thionine. Can this staining property be peculiar to this kind of cells ?

Metachromasia was originally advocated by P. Ehrlich, meaning that the dyes of the same chemical lineage stained different tissue elements in different colors. Thionine is one of the so-called "metachromatische Farbstoffe", and the mast cell granules are regarded as belonging to one sort of the "chromotrope Gewebselemente".

Concerning the other elements stained metachromatically with thionine, Hempelmann mentions the intercellular matrix of cartilage, arterial walls undergoing mucoidal degeneration, ground substance of heart valves, sclera, tendon, intracellular

mucus, secretions of epithelial mucous glands, Wharton's jelly, and mucoid substance in egg yolk. In our study, there is no need of taking these tissue elements into consideration.

In 1877 P. Ehrlich introduced the term "mast cell" and showed that the existence of intracellular granules stained metachromatically with thionine is an essential characteristic of this cell. The mast cells are spherical, ovoid, pyramidal or star-shaped, and sometimes have the elongated and attenuated processes and sometimes have the vacuoles in the cytoplasm. In some cases, cytoplasm is dimly stained metachromatically with the granules dissolved. The mast cell nucleus is usually round or oval, less seldom longitudinally stretched, indented or kidney-shaped, and almost always centrally located. The typical nucleus is commonly pale-shadowy, and is said to be sometimes jet black, and sometimes in form of cartwheel with the nuclear membrane darkly stained.

Comparing these characteristics of the mast cell with those of the cell named the pancreatectomy cell, it is easily seen that the latter is not essentially different from the former.

However, it has been stressed that the nucleus of pancreatectomy cell has coarse and darkly stained chromatin granules or a densely stained nuclear membrane. The typical nucleus of the mast cell is so pale as to seem unstained, but it can be darkly stained, if the cell becomes degenerated. It is possible therefore that the pancreatectomy cells are identical with the degenerative mast cells with the pycnotic nuclei and the pale cytoplasms, whose granules are lost, and also the intermediary cells on the way to degeneration. (Fig. 5. a. b. c.)

Although it is said that the "pancreatectomy cell" presents positive periodic acid Schiff reaction, we have not got any definite evidence to show that this reaction of the dog's mast cell is positive.

In the hypophysis, particularly in the posterior lobe, not only of the depancreatized dog, but also of the non-depancreatized one, the cells with pale pink cytoplasm stained diffusely for the periodic acid Schiff reaction were observed (apart from the endothelial cells of the blood vessels or the plasma cells), but their number seemed not so large as compared with that of the cells stained metachromatically with thionine. It is quite doubtfull whether the cells positive for the periodic acid Schiff reaction (by Yoshioka and his associates) are the same with the ones stained metachromatically with thionine.

Lillie (1950), in examining the periodic acid Schiff reaction of the mast cell, identified the mast cell, in the first place, with thionine staining, and then, by the periodic acid Schiff reaction after decolourization of the same section. Such carefulness is necessary for periodic acid Shiff reaction. Thus one may not unreasonably conclude that the so-called pancreatectomy cells are nothing but the mast cells which usually appear in the hypophysis, even if one is not sure on the periodic acid Schiff reaction.

We believe that Yoshioka and Kusama mistook Ehrlich's mast cell for the "pancreatectomy cell" and that such special cells named "pancreatectomy cell" do not

appear in the hypophysis after total pancreatectomy.

However, the fact that the tissue mast cells are found abundantly only in the hypophysis, and not in the brain substance offers a very interesting problem to be investigated.

Moreover, it seems to deserve further investigation that hyperplasia and hypertrophia of the mast cells (in another words, heparinocytes or the histaminocytes), and marked infiltration of plasma cells are to be observed in many instances in the hypophysis at a certain period after abdominal operation, especially pancreas operation.

SUMMARY

1. Yoshioka and Kusama's pancreatectomy cells are nothing but the mast cells which happen to appear in the hypophysis after total pancreatectomy.
2. These tissue mast cells are widely distributed in the hypophysis of the normal dog, (even to the upper end of the infundibulum), but not in the brain substance.
3. In the hypophysis at a certain period after total pancreatectomy and pancreatoenterostomy, one can observe in some instances, hyperplasia and hypertrophia of the tissue mast cells and marked infiltration of the plasma cells.
4. Up to the present time one has failed to recognize the appearance of any special cells in the hypophysis after pancreatectomy comparable to the castration cells or the thyroidectomy ones.

In conclusion, our deep gratitude to Prof. Dr. C. Araki and Dr. S. Amano (Department of Pathology) should be expressed for their guidance throughout the present research.

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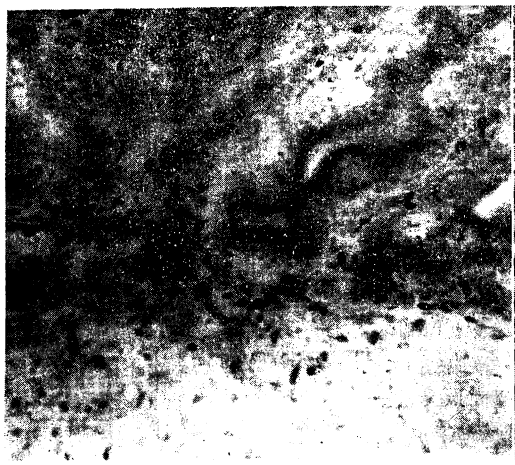

Fig. 1. : The hypophysis (pars tuberalis) of the pancreato-enterostomized dog. Mast cells are distributed in black spots.
Thionine stain, ×200

Fig. 2. : Another parts of the same hypophysis as in Fig. 1. Plasma cells are seen in groups around the transitional zone between the intermediate lobe and the posterior lobe.
Thionine stain, ×200

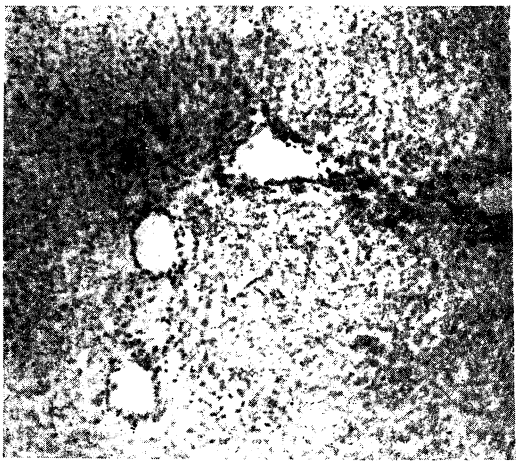

Fig. 3. : The liver of a normal dog. Mast cells are seen in black spots around blood vessels and, a few of them, in the lobule.
Thionine stain, ×100

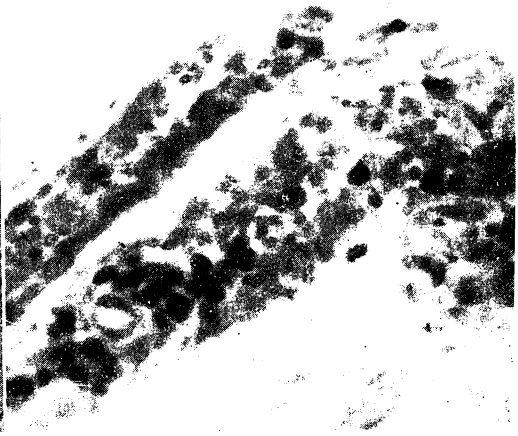

Fig. 4. : The omentum majus of the same pancreato-enterostomized dog as in Fig. 1. Plasma cells around the small blood vessel on the lower left and dark coloured mast cells on the right. Thionine stain, ×400

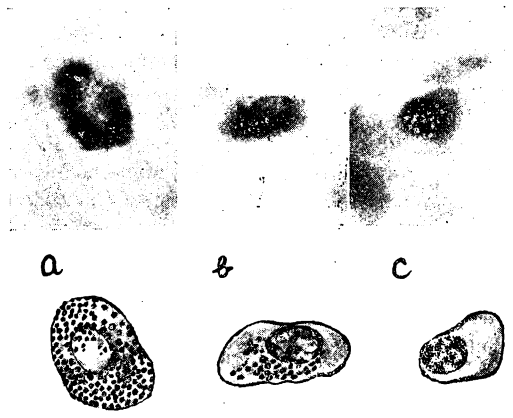

Fig. 5. : The degenerative process of the mast cells presented in Fig.1. Thionine stain, ×1000
a : Typical mast cell with a pale-shadowy nucleus and many granules.
b : Granules decrease in number and the nuclear membrane is darkly stained.
c : A degenerative mast cell with a jet black nucleus and pale cytoplasm having no granules in it.

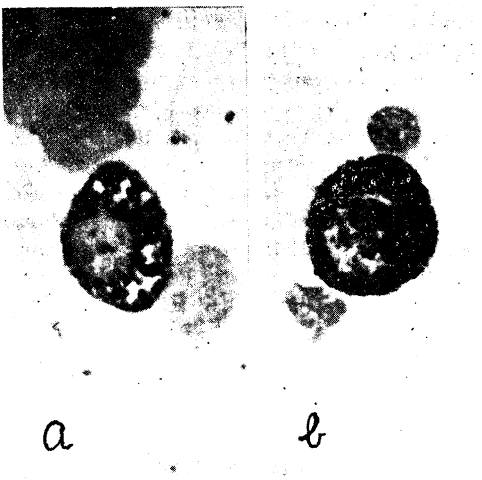

Fig. 6. a : A mast cell found in imprint of pituitary in a normal dog.
b : The same cell in imprint of the mesterial lymph node in the dog mentioabove. May-Grünwald-Giemsa stain, ×10